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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,214	09/24/2003	Alan K. Smith	216499US55CONT	1574

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	02/26/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 02/26/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/668,214	SMITH ET AL.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-71,73-75 and 77-86* is/are pending in the application.

4a) Of the above claim(s) *84-86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66-71, 73-75, 77-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 11/28/06 is acknowledged.

Claims 66-71, 73-75, 77-86 are pending.

2. Claims 84-86 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

3. Applicant's submission of Terminal Disclaimer has obviated the previous rejection of claims 66-71, 73-75, 77-83 under the judicially created doctrine of obviousness-type double patenting over claims 1-18 of U.S. Patent No. 6,835,5662.

Claims 66-71, 73-75, 77-83 read on method of providing a therapeutic benefit to a patient comprising culturing mesenchymal cells in a liquid culture medium which is replaced at a rate of at least 25% daily for more than one day and transferring said cultured cells into said patient are under consideration in the instant application.

In view of the amendment, filed 11/28/06 the following rejections remain:

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 66-71, 73-75, 77-83 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for obtaining lineage committed human cell with enhanced biological function and/or enhanced proliferation, wherein human cells are lineage committed hematopoietic cells and dendritic cells (DC) and wherein said biological function is ability of DC to stimulate T-cells *in vitro* , does not reasonably provide enablement for a method of providing a therapeutic benefit to in a patient, comprising culturing mature human cells in a liquid culture medium which is replaced at a rate of at least 25% daily for more

than one day and transferring said cultured cells with enhanced biological function into said patient, wherein said cells are programmed to develop into any specific type of tissue.
The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action, mailed on 11/04/05.

Applicant's arguments, filed 11/28/06 have been fully considered, but have not been found convincing.

Applicant asserts that (i) because cells which are cultured according to the conditions claimed are more potent, these cells have a far greater capacity to be used in therapeutic application wherever such cells are used; (ii) several provided publications further confirmed the uses of mature cells for the benefits of therapy.

Contrary to Applicant's assertion, the issue raised in the previous Office Action, was not about benefits of using cells in therapy.

As has been stated in the previous Office Action, the specification only discloses detailed *in vitro* studies of: (i) enhanced proliferative potential of T cells that may produce higher levels of particular cytokines on per cell basis (see Examples 1 and 2 in particular) and (ii) the enhanced ability of DC that were cultured under very specific growth condition in the alloMLR compared to dendritic cells grown under static culture conditions to stimulate T-cells (see example 3 in particular). The Specification does not teach or even define what is a therapeutic benefit and how it can be asserted that said therapeutic benefit, if any has been achieved after administering to a patient a cultured mature cells, wherein said cells has been cultured in a liquid culture medium which was replaced at a rate of at least 25% daily for more than one day. Moreover, the Specification defined biological function as " the ability of a cell population to carry outs its biological mission, i.e. to performed its recognized biological purpose *in vivo*" (see overlapping pages 10- 11 of the instant specification in particular.) However, it is noted that the specification does not adequately teaches or provide any examples of any therapeutic benefit that has been achieved by administering to the patient mature human cells that has been cultured in a liquid culture medium which is replaced at a rate of at least 25% daily for more than one day and transferring said cultured cells with enhanced biological function to said patient.
Moreover, the Specification does not even define what biological function, besides stimulating activity of dendritic cells *in vitro,* would be enhanced. Applicant has not exemplified any *in vivo or in vitro* studies, wherein claimed method results in enhanced of *any* biological function of human cells and used it in the method of providing any therapeutic benefit. The specification does not adequately teach how to effectively generate any tissue in a patient, comprising transferring mature human cells, that has been culturing in a liquid culture medium which is replaced at a rate of at least 25% daily for more than one day . Peshwa (WO'97/03186) teaches that there appear to be a significant difference in the characteristics of

dendritic cells their function and properties (see entire document, page 2 in particular). Engleman (WO 97/22349) teaches that biological function of dendritic cells depends on the tissue from which they were separated and that depending on cultured conditions the function may be different and that *in vitro* data does not always correlates with in vivo studies of human dendritic cells (entire document, page 6 in particular) . In addition, Cochlovius et al (Modern Drug Discovery, 2003, pages 33-38) teach that in contrast to in vitro models, and partly animal-human xenograft systems, tissue cells in vivo seems to express molecules for defense against cellular immune systems as well as against complement. Although these defense mechanisms are still poorly understood, they provide some hints as to why many potential therapeutics perform marvelously *in vitro* but a fairly high portion of them still fail *in vivo.*

Since there is no *in vivo* studies and data in the specification to show the effectively of a method of providing a therapeutic benefit to in a patient, comprising culturing mature human cells in a liquid culture medium which is replaced at a rate of at least 25% daily for more than one day and transferring said cultured cells with enhanced biological function into said patient, wherein said cells are programmed to develop into any specific type of tissue it is unpredictable how to correlate *in vitro* results with *in vivo* use. This, although the Specification describes certain *in vitro* experiments, there is no correlation on this record between *in vitro* experiments and in vivo use. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to efficacy in humans or animals (emphasis added). Ex parte Maas, 9 USPQ2d 1746.

With regards to Applicant's comments that several provided publications further confirmed the uses of mature cells for the benefits of therapy.

As has been stated supra, the issue raised by the Examiner was not about a general knowledge in the art of possible benefits of cell transplantation. The Examiner acknowledge that all of the references provided by Applicant teaches that cells transplantation might be useful for certain therapies. However, it is noted that none of said references teaches the therapeutic benefit of administering mature human cells with enhanced biological function, as claimed in the instant claims.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of providing a therapeutic benefit to in a patient, comprising culturing mature human cells in a liquid culture medium which is replaced at a rate of at least 25% daily for more than one day and transferring said cultured cells with enhanced biological function into said patient, wherein said cells are programmed to develop into any specific type of tissue in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 66-71, 73-75, 77-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,994,126 or US Patent 5,437,994 each in view of a teaching of the instant Specification on page 11.

US Patent '126 teaches a method of obtaining lineage committed human cells comprising culturing said cells under physiologically acceptable liquid culture conditions including replacement of the liquid culture medium at a rate and for a time sufficient to obtained cells suitable for various immunological intervention and treatment of diseases and transferring said cultured cells into a patient (see entire document, column 12, lines 55-65, column 13, lines 10-25, column 15, line 54-65 and column 21, line 29-35 in particular). It would immediately obvious to one skill in the art that administering of said human cells would provide a therapeutic benefit to a patient. US Patent '126 teachers that media replaced every other day for about $5x10^5$ cells/ml culture(see column 17, lines 60-65 and Example 1 in particular). US Patent '126 teachers that culture medium is any culture medium suitable for growing human cells for example RPMI (see column 16, lines 15-65 and Examples 1 and 2 in particular) . Said medium would obviously contained animal serum , glucose, lactate, glutamine and ammonia. It is noted that US Patent '126 teaches does not explicitly teaches that said cells have an enhanced biological function as compared to the function of the lineage committed cell cultured *ex-vivo*

under conditions which do not include replacement of the liquid culture. However, it is noted that the referenced cells are human cells that have been cultured under the same culturing conditions as claimed thus obviously would have an enhanced biological function *in vitro*. Moreover, it is noted that the specification on page 11, first paragraph disclosed that one skill in the art will readily appreciate that the term "biological function" refers to ability of a cell population to carry out its biological missions, i.e. for example the ability to proliferate leading to development/regeneration of tissue. Thus, it would be immediately obvious to one skill in the art that the referenced cell with enhanced biological function includes the ability to generate tissue. It is also noted Discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. " The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art". See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed.

US Patent '994 teaches a method of obtaining lineage committed human cells comprising culturing said cells under physiologically acceptable liquid culture conditions including replacement of the liquid culture medium at a rate and for a time sufficient to obtained cells suitable for various immunological intervention and treatment of diseases and transferring said cultured cells into a patient (see entire document, column 4, lines 40-65overlapping columns 5 and 6 in particular).). It would immediately obvious to one skill in the art that administering of said human cells would provide a therapeutic benefit to a patient. US Patent '994 teachers that media is replaced either continuoulsly or periodically for the cell culture at a density of $2x10^4$ to $2x10^6$.(see column column 6, lines 1-10 and overlapping columns 16-18 in particular). US Patent '994 teachers that culture medium is any culture medium suitable for growing human cells for example DMEM, IMDM, RPMI (see column 5, lines 25-40, overlapping columns 8-15 in particular) . Said medium would obviously contained animal serum , glucose lactate glutamine and ammonia. It is noted that US Patent '994 does not explicitly teaches that said cells have an enhanced biological function as compared to the function of the lineage committed cell cultured *ex-vivo* under conditions which do not include replacement of the liquid culture. However, it is noted that the referenced cells are human cells that have been cultured under the same culturing conditions as claimed thus obviously would have an enhanced biological function *in vitro*. Moreover, it is noted that the specification on page 11, first paragraph disclosed that one skill in the art will readily appreciate that the term "biological function" refers to ability of a cell population to carry out its biological missions, i.e. for example the ability to proliferate leading to development/regeneration of tissue. Thus, it would be immediately obvious to one skill in the art that the referenced cell with enhanced biological function includes the ability to generate tissue. It is also noted Discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. " The Court further held that "this same reasoning holds true when it is not a property but an ingredient which

is inherently contained in the prior art". See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed.

The claimed invention differs from the reference teaching in that US Patent '126 and US Patent '994 does not explicitly teach that the culture medium is replaced daily at the rate of at least 25%, 50% to 100% for the cell density from $1x10^4$ to $1x\ 10^7$ cell per ml of culture .

It is noted however, that prior art references teach a culturing condition, wherein the medium is continuously perfused. In other words, they teach the culturing condition wherein culture medium is replaced. Thus, it would require only routine experimentation for a person of ordinary skill in the art to determine the optimum rate of replacement of the medium, i.e. at a rate of 25% or 50% or from 25% to 100% . Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 66-71, 73-75, 77-83 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-7, 10-12, 38-41, 49-58 and 60-65 of copending Application No. 09/027,671 as is evidenced by disclosure of the specification on page 11 first paragraph. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 6-7, 10-12, 38-41, 49-58 and 60-65 of copending Application No. 09/027,671 recites a method of obtaining lineage committed human cells with enhanced biological function comprising culturing said cells under physiological conditions , said conditions including daily replacement a liquid culture medium at a rate from 50 to 100% for a cell density from $1x10^4$ to $1x10^7$ cell per ml of culture.

As is evidenced by the disclosure of the specification on page 11 first paragraph, the term "biological function" refers to ability of a cell population to carry out its biological missions, i.e. for example the ability to proliferate leading to development/regeneration of tissue. Thus, it would be immediately obvious to one skill in the art that the referenced cell with enhanced biological function includes the ability to generate tissue.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant requested that said rejection be held in abeyance since the conflicting claims have not yet been patented.

The following new grounds of rejection is necessitated by the amendment filed 11/28/06

10 . The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 74 and 75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12 Dependent claim 74 recites " said human lineage committed tissue cells ...". There is insufficient antecedent basis for this limitation in the claims, since base Claim 66 does not recite "human lineage committed tissue cells".

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MICHAIL BELYAVSKYI, PH.D.
PATENT EXAMINER

2/16/07